PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

To:

see form PCT/ISA/220

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)* see form PCT/ISA/210 (second sheet)	
Applicant's or agent's file reference see form PCT/ISA/220	**FOR FURTHER ACTION** See paragraph 2 below
International application No. PCT/EP2005/051211	International filing date *(day/month/year)* 16.03.2005
Priority date *(day/month/year)* 17.03.2004	
International Patent Classification (IPC) or both national classification and IPC C07D491/14, A61K31/437	
Applicant ALTANA PHARMA AG	

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:

European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Authorized Officer

Fink, D

Telephone No. +49 89 2399-8701

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/EP2005/051211

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 1-8 (all partly), 9, 10 (partly), 11 (partly), 12, 13, 14 (partly), 15-19, 20 (partly), 21 (partly)

because:

☒ the said international application, or the said claims Nos. 21 (as regards industrial applicability) relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the whole application or for said claims Nos. 1-8 (all partly), 9, 10 (partly), 11 (partly), 12, 13, 14 (partly), 15-19, 20 (partly), 21 (partly)

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/EP2005/051211

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has:

   ☐ paid additional fees.

   ☐ paid additional fees under protest.

   ☒ not paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is

   ☐ complied with

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☐ all parts.

   ☒ the parts relating to claims Nos. 1-8 (all partly), 10 (partly), 11 (partly), 14 (partly), 20 (partly), 21 (partly)

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-8 (all partly), 10 (partly), 11 (partly), 14 (partly), 20 (partly), 21 (partly)
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-8, 10, 11, 14, 20, 21
Industrial applicability (IA)	Yes:	Claims	1-8 (all partly), 10 (partly), 11 (partly), 14 (partly), 20 (partly)
	No:	Claims	

2. Citations and explanations

   see separate sheet

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (SEPARATE SHEET)

International application No.
PCT/EP2005/051211

Re Item III.

1. The present **claim 21** relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT.
Consequently, no opinion will be formulated with respect to industrial applicability of the subject-matter of this claim.

[For the assessment of the aforesaid claim on the question whether it is industrially applicable, no unified criteria exist in the PCT. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but will allow, however, claims to a (known) *compound for* first *use in medical treatment* and the *use* of such a compound *for the manufacture of a medicament* for a new medical treatment.]

2. The present application was found to be *non-unitary* in the sense of Rule 13 PCT (see, the **item IV** below).
The search has therefore been limited to the first present invention, i.e. to the compounds of the present claim 1 wherein the group R2 is ***hydroxy-3-4-C-alkenyl*** or ***hydroxy-3-4C-alkinyl***.
Accordingly, the Partial International Search Report (PISR) was only complete with respect to the present claims 1-8 (all partly), 10 (partly), 11 (partly), 14 (partly), 20 (partly) and 21 (partly).
As the PISR forms the basis of the present Written Opinion, the following statement on the patentability of the present subject-matter can only be regarded to be complete in respect of the said **claims 1-8** (all **partly**), **10 (partly)**, **11 (partly)**, **14 (partly)**, **20 (partly)** and **21 (partly)**.
In so far as the following letter refers to claims 1-8, 10, 11, 14, 20 and 21, it should only be taken to refer to the searched scope of these claims.

Re Item IV.

The present application lacks unity within the meaning of Rule 13 PCT for the following reasons:

The document WO-A-03/014123 (**D1**) - which represents the **closest prior art** - discloses (cf., pages 26-27, claim 1) i.a. 2,3-disubstituted 9-phenyl-7H-8,9-dihydro-pyrano[2,3-c]imidazo[1,2-a]pyridine-6-carboxylic acid amides which are said to have *gastric acid secretion-inhibitory* activity (cf., page 29, claim 8; and page 24, table A).

More specifically, **D1** teaches, for instance, the compound 2,*3*-Di*methyl*-9-phenyl-7H-8,9-dihydro-pyrano[2,3-c]imidazo[1,2-a]pyridine-6-carboxylic acid dimethylamide (see, the example 3 on pages 13-14) which is excluded from the present **claims 1-3** by way of proviso.

In the light of **D1**, the **problem** underlying the present application resides in the provision of further (alternative) *gastric acid secretion-inhibitors* of the 9-phenyl-7H-8,9-dihydro-pyrano[2,3-c]imidazo[1,2-a]pyridine type.

Accordingly, the present application proposes the 3- and/or 6- substituted 9-Arom-7H-8,9-dihydro-pyrano[2,3-c]imidazo[1,2-a]pyridine derivatives of the present formula (1) in order to **solve** the given problem.

The only structural feature discernible, which is **shared by all** of the compounds of the formula (1) according to the present claim 1 is the

6-(R3)-9-Arom-7H-8,9-dihydro-pyrano[2,3-c]imidazo[1,2-a]pyridine

moiety (wherein R3 and Arom are as defined in the present claim 1).

The document **D1**, however, already describes such 6-substituted 9-phenyl-7H-8,9-dihydro-pyrano[2,3-c]imidazo[1,2-a]pyridine compounds (cf., for example, the 2,3-Di*methyl*-9-phenyl-7H-8,9-dihydro-pyrano[2,3-c]imidazo[1,2-a]pyridine-6-*carboxylic acid dimethylamide* of the example 3 of **D1**) ***for the same use*** as the compounds according to the present application.

As the only structural feature which is **common to all** of the present compounds (i.e. the 6-(R3)-9-Arom-7H-8,9-dihydro-pyrano[2,3-c]imidazo[1,2-a]pyridine moiety) is **not novel** (cf. **D1**), this structural feature cannot represent the "special technical feature" within the meaning of Rule 13.2 PCT.

The present application thus relates to different solutions to the given technical problem (i.e., the provision of further *gastric acid secretion-inhibitors*) which are not linked by a single general inventive concept as set forth in Article 13 PCT.

Hence the Search Division considers that the following **21** separate inventions or groups of inventions are not so linked as to form a single general inventive concept:

1. the compounds of the present claim 1 wherein the group R2 is ***hydroxy-3-4-C-alkenyl*** or ***hydroxy-3-4C-alkinyl*** (which differ from the compounds of **D1** in that they have a 3-(hydroxy-3-4-C-*alkenyl/alkinyl*) group rather than a 3-(hydroxy-1-4C-*alkyl*) group (cf., claim 1 of **D1**));

2. the compounds of the present claim 1 wherein the group R2 is ***hydroxy*** or ***1-4C-alkoxy*** (which differ from the compounds of **D1** in that they have a *3-oxy*-substituent rather than a 3-(1-4C-*alkyl*) group (cf., claim 1 of **D1**));

3. the compounds of the present claim 1 wherein the group R2 is ***amino***, ***mono-*** or ***di-1-4C-alkylamino***, ***1-4C-alkylcarbonylamino***, ***1-4C-alkoxy-carbonylamino***, or ***1-4C-alkoxy-1-4C-alkoxycarbonylamino*** (which differ from the compounds of **D1** in that they have a *3-amino*-substituent rather than a 3-(1-4C-*alkyl*) group (cf., claim 1 of **D1**));

4. the compounds of the present claim 1 wherein the group R2 is ***carboxyl*** (which differ from the compounds of **D1** in that they have a *3-carboxyl* group rather than a 3-(1-4C-*alkoxycarbonyl*) group (cf., claim 1 of **D1**));

5. the compounds of the present claim 1 wherein the group R2 is ***mono-*** or ***di-1-4C-alkylamino-1-4C-alkyl*** (which differ from the compounds of **D1** in that they have a 3-(alkyl*amino*-1-4-C-alkyl) group rather than a 3-(*hydroxy*-1-4C-alkyl) group (cf., claim 1 of **D1**));

6. the compounds of the present claim 1 wherein the group R2 is ***1-4C-alkylcarbonyl***, ***2-4C-alkenylcarbonyl***, or ***2-4C-alkinylcarbonyl*** (which differ from the compounds of **D1** in that they have a *3-acyl* group rather than a 3-(1-4C-*alkyl*) group (cf., claim 1 of **D1**));

7. the compounds of the present claim 1 wherein the group R2 is the radical ***-CO-NR21R22*** (which differ from the compounds of **D1** in that they have a 3-*carbamoyl* group rather than a 3-(1-4C-*alkoxycarbonyl*) group (cf., claim 1 of **D1**));

8. the compounds of the present claim 1 wherein the group R2 is as defined in **D1**, and R3 is ***1-4C-alkylcarbonyl*** (which differ from the compounds of **D1** in that they have a *6-(1-4C-alkyl*carbonyl) group rather than a 6-(*1-4C-alkoxy*carbonyl) group (cf., claim 1 of **D1**));

9. the compounds of the present claim 1 wherein the group R2 is as defined in **D1**, and R3 is ***cyano*** (which differ from the compounds of **D1** in that they have a *6-cyano* group rather than a 6-*carbamoyl* group (cf., claim 1 of **D1**));

10. the compounds of the present claim 1 wherein the group R2 is as defined in **D1**, and R3 is the radical ***-CO-NR31R32*** wherein R31 is ***amino*** (which differ from the compounds of **D1** in that they have a 6-*hydrazino*carbonyl group rather than a 6-*carbamoyl* group (cf., claim 1 of **D1**));

11. the compounds of the present claim 1 wherein the group R2 is as defined in **D1**, and R3 is the radical ***-CO-NR31R32*** wherein R31 is ***hydroxy*** or ***1-4C-alkoxy*** (which differ from the compounds of **D1** in that they have a 6-(*N-(hydroxy / 1-4C-alkoxy)*carbamoyl) group rather than a 6-carbamoyl group (cf., claim 1 of **D1**));

12. the compounds of the present claim 1 wherein the group R2 is as defined in **D1**, and R3 is the radical ***-CO-NR31R32*** wherein R31 is ***3-7C-cycloalkyl*** (which differ from the compounds of **D1** in that they have a 6-(N-(*3-7C-cycloalkyl*)carbamoyl) group rather than a 6-(N-(*1-7C-alkyl*)carbamoyl) group (cf., claim 1 of **D1**));

13. the compounds of the present claim 1 wherein the group R2 is as defined in **D1**, and R3 is the radical ***-CO-NR31R32*** wherein R31 is ***1-4C-alkylsulfonyl***, ***arylsulfonyl***, or ***aryl-1-4C-alkylsulfonyl*** (which differ from the compounds of **D1** in that they have a 6-(*sulfonylamino*carbonyl group rather than a 6-*carbamoyl* group

(cf., claim 1 of **D1**));

14. the compounds of the present claim 1 wherein the group R2 is as defined in **D1**, and R3 is the radical ***-CO-NR31R32*** wherein R31 is ***aryl*** (which differ from the compounds of **D1** in that they have a 6-(N-(*aryl*)carbamoyl) group rather than a 6-(N-(*1-7C-alkyl*)carbamoyl) group (cf., claim 1 of **D1**));

15. the compounds of the present claim 1 wherein the group R2 is as defined in **D1**, and R3 is the radical ***-CO-NR31R32*** wherein R31 and R32 together and including the nitrogen atom to which they are attached form a ***pyrrolidino***, ***piperidino***, or ***morpholino*** radical which is ***substituted by R33***, ***R34***, and ***R35*** where at least one of the substituents R33, R34, or R35 has to be ***different from hydrogen*** (which differ from the compounds of **D1** in that they have a 6-((*substituted* pyrrolidino/piperidino/morpholino)carbonyl) group rather than a 6-((*unsubstituted* pyrrolidino/piperidino/morpholino) carbonyl) group (cf., claim 1 of **D1**));

16. the compounds of the present claim 1 wherein the group R2 is as defined in **D1**, and R3 is the radical ***-CO-NR31R32*** wherein R31 and R32 together and including the nitrogen atom to which they are attached form a ***piperazino*** radical (which differ from the compounds of **D1** in that they have a 6-(*piperazino*carbonyl) group rather than a 6-(*morpholino*carbonyl) group (cf., claim 1 of **D1**));

17. the compounds of the present claim 1 wherein the group R2 is as defined in **D1**, and R3 is the radical ***-CO-NR31R32*** wherein R31 and R32 together and including the nitrogen atom to which they are attached form a ***aziridino*** or ***azetidino*** radical (which differ from the compounds of **D1** in that they have a 6-((*aziridino/azetidino*)carbonyl) group rather than a 6-((*pyrrolidino*)carbonyl) group (cf., claim 1 of **D1**));

18. the compounds of the present claim 1 wherein the group R2 is as defined in **D1**, and R3 is the radical ***-SO_2-NR31R32*** (which differ from the compounds of **D1** in that they have a 6-*sulfamoyl* group rather than a 6-*carbamoyl* group (cf., claim 1 of **D1**));

19. the compounds of the present claim 1 wherein the group R2 is as defined in **D1**, and R3 is the radical ***-CS-NR31R32*** (which differ from the compounds of **D1** in that they have a 6-*thio*carbamoyl group rather than a 6-carbamoyl group (cf., claim 1 of **D1**));

20. the compounds of the present claim 1 wherein the group R2 is as defined in **D1**, and R3 is the radical ***-C=N(OH)-NR31R32*** (which differ from the compounds of **D1** in that they have a 6-(*N-hydroxyamidino*) group rather than a 6-carbamoyl group (cf., claim 1 of **D1**));

21. the compounds of the present claim 1 wherein the group R2 is as defined in **D1**, and R3 is the group ***Het*** (which differ from the compounds of **D1** in that they have a 6-(*5-membered N-containing heterocycyl*) group rather than a 6-*carbamoyl* group (cf., claim 1 of **D1**));

(The different inventions / groups of inventions were formulated in the order chosen by the Applicant). The separate inventions/groups of inventions are:

Re Item V.

The following documents (D) are considered to be relevant:

D1: ..... WO-A-03/014123 (20 February 2003);
D2: ..... WO-A-95/27714 (19 October 1995);
D3: ..... *Journal of Medicinal Chemistry* **28**(7), 876-892 (1985);

1. NOVELTY (Article 33(2) PCT):

The present application satisfies the criterion set forth in Article 33(2) PCT because the subject-matter of **claims 1-8, 10, 11, 14, 20** and **21** is new in respect of prior art as defined in the regulations (Rule 64(1)-(3) PCT):

The 7H-8,9-dihydro-pyrano[2,3-c]imidazo[1,2-a]pyridine derivatives of the present independent **claim 1** are novel over the 7H-8,9-dihydro-pyrano[2,3-c]imidazo[1,2-a]pyridine compounds of **D1** on account of the present ***proviso*** (which excludes the compounds of claim 1 of **D1**).

They are furthermore novel over **D2** (cf., claim 1 therein) on account of the present substituent group ***R3*** (the present 7H-8,9-dihydro-pyrano[2,3-c]imidazo[1,2-a]pyridine derivatives have to be ***substituted*** at the ***6-position*** whereas **D2** relates to *6-unsubstituted* 7H-8,9-dihydro-pyrano[2,3-c]imidazo[1,2-a]pyridine compounds).

The prior art **D3** teaches (cf., the compounds of table IV) imidazo[1,2-a]pyridine derivatives. The present ***7H-8,9-dihydro-pyrano[2,3-c]***imidazo[1,2-a]pyridine are thus also novel over **D3**.

2. INVENTIVE STEP (Article 33(3) PCT):

The present application does not satisfy the criterion set forth in Article 33(3) PCT because the subject-matter of **claims 1-8, 10, 11, 14, 20** and **21** does not appear to involve an inventive step (Rule 65(1)(2) PCT):

Document **D1** - which is considered to represent the **closest prior art** teaches (cf., claim 1 therein) i.a. 2,3,6-trisubstituted 9-phenyl-7H-8,9-dihydro-pyrano[2,3-c]imidazo[1,2-a]pyridine derivatives which are said to have *gastric acid secretion-inhibitory* activity (cf., claim 8 and page 24, table A).

More specifically, **D1** teaches, for instance, the compound *2,3-Dimethyl*-9-phenyl-7H-8,9-dihydro-pyrano[2,3-c]imidazo[1,2-a]pyridine-*6-carboxylic acid dimethylamide* (see, the example 3).

The compounds of claim 1 of **D1** are excluded from the present **claim 1** by the present proviso.

In the light of **D1**, the **problem** underlying the present application resides in the provision of further (alternative) *gastric acid secretion-inhibitors* of the 7H-8,9-dihydro-pyrano[2,3-c]imidazo[1,2-a]pyridine type.

Accordingly, the present application proposes the 3-(*hydroxy-3-4C-alkenyl / hydroxy-3-4C-alkynyl*)-7H-8,9-dihydro-pyrano[2,3-c]imidazo[1,2-a]pyridine derivatives according to the present **claim 1** in order to **solve** the given problem.

This solution cannot, however, be considered to involve an inventive step (Article 33(3) PCT) for the following reasons:

As the document **D1** already teaches the *gastric acid secretion-inhibitory* activity of

(i) 3-(***1-4C-alkyl***)-7H-8,9-dihydro-pyrano[2,3-c]imidazo[1,2-a]pyridine and
(ii) 3-(***2-4C-alkenyl / 2-4C-alkynyl***)-7H-8,9-dihydro-pyrano[2,3-c]imidazo[1,2-a]pyridine derivatives, on the one hand, and
(iii) 3-(***hydroxy****-1-4C-alkyl*)-7H-8,9-dihydro-pyrano[2,3-c]imidazo[1,2-a]pyridine derivatives (cf., the definition of the substituent group R2), on the other hand,

it is considered that the person skilled in the art would have expected that the corresponding 3-(***hydroxy****-2-4C-alkenyl / 2-4C-alkynyl*)-7H-8,9-dihydro-pyrano[2,3-c]imidazo[1,2-a]pyridine derivatives would also possess (some) *gastric acid secretion-inhibitory* activity.

It is therefore considered that the present solution (i.e., the 3-(*hydroxy-3-4C-alkenyl / hydroxy-3-4C-alkynyl*)-7H-8,9-dihydro-pyrano[2,3-c]imidazo[1,2-a]pyridine derivatives according to the present **claims 1-8, 10, 11** and **14**) has to be regarded to be **obvious** in the light of the teaching of **D1**.

Consequently, in the absence of any **unexpected / surprising effect**, the subject-matter of the present **claims 1-8, 10, 11, 14, 20** and **21** cannot be regarded to involve an inventive step as set forth in Article 33(3) PCT.

3. INDUSTRIAL APPLICABILITY (Article 33(4) PCT):

The subject-matter of the present **claims 1-8, 10, 11, 14** and **20** concerns chemical compounds and a pharmaceutical composition and is therefore considered to be industrial applicable in the sense of Article 33(4) PCT.

4. MISCELLANEOUS:

The citation of the prior art **D3** on page 1, lines 13-14 should have (also) included a reference to the *gastric antisecretory* properties of the said imidazopyridine compounds of **D3**.